REMARKS

Claims 29, and 41-61 are pending. By this amendment, several claims have been amended without introducing new matter. Claims 29, and 41-61 remain pending.

IDS

Paragraph 1 of the Office Action indicates that the IDS filed May 10, 2005 has been considered. Applicants note, however, that although the Examiner has signed and dated the form PTO/SB/08b, he has not initialed or checked each reference thereby indicating each reference has been considered. Applicants respectfully request that the Examiner initial form PTO/SB/08b where indicated so the record accurately reflects that these references have been considered and that an initialed copy is sent to Applicants with the next communication from the Office.

Applicants note that two references (WO2001/94582 and WO2003/027142) provided in the December 6, 2004 IDS, form PTO/SB/08a have not been indicated as considered but have been marked "no translation." Applicants respectfully submit that each of these references were submitted with the indication that there was indeed an English Abstract only. MPEP § 609 III.A.(3) indicates, that an English Abstract may suffice as the concise explanation of a reference that is in a non-English language. Accordingly, Applicants respectfully submit that they have met their duty of candor with the Office and respectfully request that the references be considered on the record. Nevertheless, in the spirit of cooperation and an abundance of caution with respect to the duty to the Office, Applicants submit herewith an IDS providing US2004029224, which is the US version of WO2001/94582. According to Applicants' search (on esp@ce.net) WO2003/027142 has no English-language equivalent. Accordingly, the English Abstract has already been provided in satisfaction of the requirement for a concise statement for non-English language references. Consideration of the references on the record is respectfully requested.

The Office Action

The Action contains a section entitled "Response to Applicants arguments" which contains a new 35 U.S.C. § 112 rejection of claims 41, 43, and 45 in paragraph 3, and addresses Applicants' prior discussion regarding utility in paragraph 4. The Examiner's comments with regard to utility will be addressed in responding to the current rejections based thereon. The

Action continues, with discussions on current rejections under 35 U.S.C. § 112 second paragraph, 35 U.S.C. §§ 101 and 112, and 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, first paragraph

Claims 41, 43, and 45 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The rejection objects to the amended language "associated with sensorimotor processing or arousal disorder." Applicants have deleted this language. Applicants respectfully submit that these deletions are made as an administrative expedient and that the specification clearly supports the association of hRUP35 with the thalamus and sensorimotor processing and arousal disorders. The discussion, however, is moot in light of the current amendments. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 41-43 and 46-56 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite.

Claims 41, 43, and 45 are allegedly indefinite because "it is not clear what is the association of the G-protein coupled receptor to sensorimotor processing or arousal disorder." Applicants respectfully assert that although they believe the claims to be clear and definite, the amendments discussed above, deleting the questioned language, render the current rejection moot.

Claims 42 and 46-56 are allegedly indefinite because they depend from the claims rejected above. Accordingly, the rejection of these claims is moot as discussed above.

Withdrawal of the 35 U.S.C. § 112, second paragraph rejections is respectfully requested.

35 U.S.C. §§ 101 and 112, 1st paragraph

The rejection of claims 29, and 41-56 under 35 U.S.C. § 101 and 112 was maintained for the reasons of record, which were also applied to additional claims 57-61.

As with many rejections based on utility under 35 U.S.C. § 101, this rejection is a lengthy and dizzying array of interwoven thoughts, in this case spanning twelve and a half pages in addition to nearly 5 pages dismissively summarizing Applicants' prior response, but not really addressing the present facts or arguments of Applicants' last response.

The rejection at page 11 states, "The utilities asserted by Applicant are not specific or substantial." The bases for this conclusion are perhaps best summarized on page 6, which says (in response to Applicants' prior response) "The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention," and on page 11 which continues "the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a 'real world' context of use."

Applicants' maintain that the original rejection did not satisfy the requirements for a *prima facie* showing of a lack of utility. MPEP § 2107.02 III.A. makes it clear that the Office must presume that Applicants' statements of utility are true, and that the Office should give deference to Applicants' understanding of the invention when the statements of utility are examined. The MPEP specifically states "Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicants." "Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons."

Furthermore, the MPEP continues, stating "to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the are would doubt (i.e. "question") the truth of the statement of utility. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to uphold the rejection, the totality of the evidence must show that it is more likely than not that Applicants' statements of utility are false. This is not the case.

Applicants respectfully submit that the totality of the evidence shows that Applicants have asserted a specific, substantial and credible utility and the Office has not provided evidence that it is more likely than not that Applicants' statements of utility are false.

Applicants address the requirements of 35 U.S.C. § 101 to assert a specific, substantial and credible utility, in a straightforward manner similar to the Revised Interim Utility Guidelines

Training Materials (hereafter "Guidelines") available at http://www.uspto.gov/web/menu/utility.pdf, which pose the questions of specificity, substantiality and credibility in turn. As in the prior response, Applicants turn to Example 12 of the Guidelines as a particularly relevant guide.

1) Has the Applicant made any assertion of utility for the specifically claimed invention?

YES. Page 8 of the Action admits "Applicant has asserted utilities for the specifically claimed invention of claims 29, 41-56." The Action does not characterize these asserted utilities. Applicants respectfully assert that at least one of these utilities parallels that set forth in Example 12, namely for use in methods of identifying materials which bind to hRUP35, i.e. screening methods. Thus, at least one utility has been asserted.

2) Is the asserted utility specific?

YES. Here, Applicants simply paraphrase the answer in Guidelines Example 12:

"In this case, the method of identifying materials which bind to a specific receptor, namely [hRUP35] . . . [is a method that is] not applicable to the general class of receptors [or even the subclass of GPCRs]. Therefore, there is an asserted specific utility for the claimed invention." (modifications added.)

Applicants believe the simplicity of this analysis is a blessing and the conclusion with respect to the present case is indisputable in light of the close similarity to Guidelines Example 12 (at least with respect to the non-disclosure of a biological function), which clearly indicates that neither a biological function nor a disease state was disclosed in the Example specification, and, thus, clearly indicates neither is required to establish a specific utility.

Applicants' asserted utility is specific.

3) Is the asserted utility substantial?

YES. Here the facts of the present case begin to differ more significantly from those of Guidelines Example 12. Particularly, Guidelines Example 12 specifically states that no disease or condition is disclosed by the specification. In sharp contrast, Applicants have disclosed thalamus-related disorders, specifically, sensorimotor processing and arousal disorders. The Example does, however, provide some much needed guidance. In this case, the discussion of substantiality with respect to Guidelines Example 12, claim 2, seems to flesh out the requirement

more than the discussion related to claim 1. (Both discussions focus on the fact that the Example does not disclose any disease or body condition.) The Guidelines on page 67 state:

> Specifically, the method essentially is a method of identifying a material, i.e., those materials which bind to receptor A. Thus, to determine whether or not this method has a 'substantial' utility, it must be determined whether or not the material that binds to receptor A itself has a 'substantial utility.' Here, the only utility asserted for the identified materials is a therapeutic to effect control over receptor A. Since neither the specification nor the art of record disclose any disease states or conditions associated with receptor A, the asserted utility in this case essentially is a method of treating an unspecified, undisclosed disease or condition, which does not define a 'real world' context of use. Treating an unspecified, undisclosed disease or condition clearly would require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use. (citations omitted)

This language is repeated nearly verbatim in the current rejection. The present case, however, is easily distinguished from that set forth in Guidelines Example 12. The present utility is not merely to effect therapeutic control over hRUP35, but rather to treat sensorimotor processing and arousal disorders via that control. The present case clearly links hRUP35, through its expression in the thalamus, to sensorimotor processing disorders and arousal disorders, which were well known to those of skill in the art (see, Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996) 9th Ed, McGraw-Hill, p.465; Elble (1998) Movement Disorders, 13:35-39, Portas et al (1998) The Journal of Neuroscience, 18:8979-8989; and Jeljeli et al. (2000) Neuroscience Research, 38:155-164). It appears to Applicants that the Office's heavy reliance on its position that hRUP35 is not associated with sensorimotor processing and arousal disorders is misplaced and completely lacking in evidentiary support. Consequently, the conclusion that the utility is for treating an unspecified, undisclosed disease or condition is flawed. The facts set forth in the specification or otherwise available to those of skill in the art, and simple logic lead to the conclusion that hRUP35 is associated with sensorimotor processing and arousal disorders, and, thus, a specified, disclosed disease or condition has been associated with hRUP35. Applicants specification and/or reasoning herein establish:

a. hRUP35 is expressed in the thalamus (see Table E);

b. proteins located/expressed in the thalamus are associated with sensorimotor processing and arousal (see paragraph [0075]);

c. expression in the thalamus is associated with sensorimotor processing and arousal disorders (see paragraph [0075] and paragraph [0214] following Table E); and

d. hRUP35 expression results in increased levels of IP_3 in thalamus (see Fig. 2; OA, p. 9).

Therefore, logically, it follows that hRUP35, through its expression in the thalamus, is associated with sensorimotor processing and arousal disorders and therefore can be used to screen for compounds to treat such disorders.

Thus, compounds identified by the screening methods can be used to treat sensorimotor processing and arousal disorders. Such disorders are specific and substantial. Thus, the asserted utility of identifying compounds that bind to hRUP35 to treat these disorders is substantial.

4) Is the utility credible?

YES. The Action does not directly address credibility as a separate element. Guidelines Example 12, likewise, does not reach the question of credibility, in part, we suspect, because it settles the question of utility in its analysis under the substantial requirement.

With respect to credibility, the MPEP § 2107 and the caselaw are clear that once Applicants have asserted a specific and substantial utility, a presumption of utility must be rebutted by the Office with evidence of reasons why one of skill in the art would have doubted the utility. Here, the Office has provided no evidence as to why one of skill in the art would have questioned either the facts or logic underlying Applicants' asserted utility, and, thus, has not properly set forth a *prima facie* case of lack of utility.

Although Applicants maintain that the Office has yet to provide evidence sufficient to support a *prima facie* case of lack of utility, we note that given Applicants' prior response, the Office must assess utility in light of the totality of the record. MPEP § 2107 directs that

> **Only** where the **totality of the record** continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. (Emphasis added.)

The Office must establish that it is more likely than not that a person of ordinary skill in the art would not consider the utility asserted by Applicants to be specific and substantial. Applicants respectfully submit that the totality of the record shows that those of skill in the art would have been more likely than not to consider applicants utility to be specific and substantial.

The Action has several repeated themes throughout the lengthy Rejection:

1. Properties of hRUP35 are based solely on its membership in the highly divergent GPCR family;

2. there is no activity or function associated with hRUP35;

3. there is no association of hRUP35 with a disease or disorder and therefore the methods are directed to unspecified, undisclosed diseases or disorders; and

4. no ligand for hRUP35 is known.

Even in light of these positions those of skill in the art would not have a reason to doubt that Applicants' assertion that the GPCR hRUP35 could be used to screen for compounds useful in treating sensorimotor processing or arousal disorders. Applicants have presented facts indicating that hRUP35 is expressed in the thalamus and that expression in the thalamus is associated with sensorimotor processing and arousal. For this reason alone, the Office's allegations are not sufficient to rebut the truth of Applicants' statements of utility. The repeated themes of the rejection are either unimportant in the discussion of specific and substantial utility, or inaccurate.

Theme 1: *Properties of hRUP35 are based solely on its membership in the highly divergent GPCR family.* While it is true that hRU35 is a GPCR and, thus, has properties also attributable to other members of the group, the properties of hRUP35 are not based solely on its membership in the GPCR family. hRUP35 increases the level of intracellular IP_3, as exemplified in Fig. 2 by transfected 293 cells expressing recombinant hRUP35. Those of skill in the art viewing this data, coupled with the known expression in the thalamus would conclude that hRUP35 increases intracellular IP_3 in the thalamus. It is this expression and data, *inter alia*, that lead one skilled in the art to appreciate hRUP35's usefulness in treating sensorimoter processing and arousal disorders. Applicants do NOT rely solely on the fact that hRUP35 is a GPCR. This

theme seems to be directed to the specific requirement of 35 U.S.C. § 101, which, as discussed above, is clearly met by Applicants.

Theme 2: *There is no activity or function associated with hRUP35.* As discussed above, to have a specific and substantial utility, there need not be a known or disclosed activity. However, Applicants have disclosed in Fig. 2 that hRUP35 expression leads to increased intracellular IP_3 levels. Those of skill in the art, at least as early as 1994, would have recognized that a GPCR expressed in thalamus can modulate sensorimotor processing and arousal and, furthermore, that a GPCR expressed in thalamus that stimulates IP_3 metabolism (e.g. increases an intracellular level of IP_3) can modulate sensorimotor processing and arousal. Applicants submit herewith a copy of Salt and Eaton, Neurochem Int (1994) 24:451-458, which teaches that a GPCR known to stimulate IP_3 metabolism modulates sensory response in thalamus, e.g. response evoked by noxious thermal stimulation of the peripheral receptive field (see, e.g. p. 455, lines 1-28 of the Discussion.) This teaching is further supported by Miyata et al., J Neurosci (2003) 23:8098-8108 (also submitted herewith). These references support the credibility of Applicants' utility, and make it more likely than not that one skilled in the art would not have questioned Applicants' asserted utility.

Theme 3: *There is no association of hRUP35 with sensorimotor processing or arousal disorders and therefore the methods are directed to unspecified, undisclosed diseases or disorders.* The specification associates sensorimotor processing and arousal with hRUP35 through its expression in the thalamus. Those of skill in the art would appreciate that hRUP35's expression in the thalamus and accompanying increase in intracellular IP_3 would make it useful in treatment of diseases/disorders of the thalamus such as sensorimotor processing and arousal disorders.

Theme 4: *No ligand for hRUP35 is known.* Knowledge of the natural ligand for a receptor is NOT a requirement for utility under 35 U.S.C. § 101. Nor would those of skill in the art doubt an asserted utility merely because the natural ligand is unknown, indeed Applicants have previously noted that other well-known receptors (e.g. the niacin receptor) agonists of which have been identified and used for years without ever deorphanizing the receptor. Those of skill in the art would appreciate Applicants' teachings linking hRUP35 expression to the

thalamus and, in turn, to thalamus-related disorders, specifically sensorimotor processing and arousal disorders. Given Applicants' teaching, the lack of a natural ligand would not lead those of skill in the art to question the asserted utility.

Thus, an examination of the totality of the record supports a finding that those of skill in the art would be more likely to believe Applicants' asserted utility, and less likely to doubt that assertion. Accordingly, the rejection cannot be maintained.

Withdrawal of the 35 U.S.C. § 101, and accompanying 35 U.S.C. § 112 rejections is respectfully requested.

Applicants' Utility is Specific, Substantial, and Credible

Applicants respectfully submit that in light of the discussion above, it is clear that Applicants' asserted utility is specific, substantial, and credible. To the extent that the Examiner maintains the rejection, it is respectfully requested that he point out to Applicants, specifically, which of the three prongs of the utility requirement is lacking and why, along with the required evidentiary support.

35 U.S.C. § 112, first paragraph

Claims 44-61 stand rejected under 35 U.S.C. § 112 for allegedly failing to comply with the enablement requirement. Paragraphs [0154] to [0157] teach how to obtain an endogenous nucleic acid sequence encoding an endogenous human RUP35 G protein-coupled receptor by carrying out RT-PCR using a pair of specific primers. Those of skill in the art will appreciate that RT-PCR employing the specific primers of SEQ ID NOs: 41 and 42 specifically amplify an endogenous nucleic acid sequence encoding an endogenous human RUP35 G protein-coupled receptor, as taught by the specification. SEQ ID NO:15 exemplifies such a nucleic acid; however, the teaching encompasses any endogenous nucleic acid encoding an endogenous RUP35 G protein-coupled receptor obtainable by carrying out RT-PCR using the pair of specific primers. For example, it encompasses an endogenous nucleic acid encoding a naturally occurring variant of SEQ ID NO: 16 that is amplifiable by the process. Applicants note that in the interest of clarity, the claim has been amended by replacing "obtainable" with "amplifiable." Thus, Applicants respectfully assert that those of skill in the art would be able to make or use the claimed invention. The enablement requirement has been satisfied.

35 U.S.C. § 112, first paragraph

Claims 44-61 are rejected under 35 U.S.C. § 112 for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of their invention. Applicants are not claiming "every polynucleotide known to man", but rather those which are amplifiable via RT-PCR with the specific pair of primers in the claim. Claim 44 has been amended to clarify that the desired nucleic acid sequence is amplifiable by RT-PCR employing the specifically claimed primers. As discussed above, this technique is applicable to any [endogenous] nucleic acid encoding an endogenous [RUP35] G protein-coupled receptor obtainable by carrying out RT-PCR using the pair of specific primers. Applicants' specification teaches and provides examples of how this process is carried out (see pages 34-35). Thus, Applicants respectfully assert that those of skill in the art would readily appreciate that Applicants were in possession of the invention.

Applicants respectfully submit that all requirements of 35 U.S.C. § 112 have been met. Withdrawal of the rejections based thereon is respectfully requested.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account 50-1275.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,

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